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09/428,122	10/27/1999	ANDREW D. MURDIN	19721-007-(P	4261

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/428,122	MURDIN ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10-14,16,18,19,25,26,38,39 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10-14,16,18,19,25,26,38,39 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence search report (1).

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 11/13/03 in response to the non-final Office Action mailed 08/20/03. With this, Applicants have amended the specification.

Status of Claims

2) Claim 1 has been amended via the amendment filed 11/13/03.

Claims 1-4, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42-44 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Maintained

5) The rejection of claim 1 made in paragraph 15(a) of the Office Action mailed 08/20/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants state that they have amended claim 1 to recite 'against infection by said strain of *Chlamydia*', which allegedly defines the metes and bounds of the claimed subject matter.

Applicants' argument has been considered, but is not persuasive. It is still not clear how a polynucleotide of SEQ ID NO: 1, a 95% sequence homolog thereof, or a polynucleotide that hybridizes under conditions recited in part (c) of the claim with SEQ ID NO: 1 can induce an immune response against infection by said strain of Chlamydia on administration to a mammal. It is unclear to what part or antigen of the chlamydial strain the immune response is directed to: polynucleotide, polypeptide, an intracellular antigen, or an extracellular antigen? If the immune response is polynucleotide-specific, it is unclear how would it be effective against infection by said strain of *Chlamydia*, since the polynucleotide is intracellular and therefore inaccessible to the

antibodies or immune cells. Is the immune response specific to the claimed polynucleotide or the polypeptide expressed in the mammal by the polynucleotide? If the latter is the case, it is unclear how a naked chlamydial polynucleotide is getting expressed in a mammalian host just by administration intranasally or intramuscularly to the host.

6) The rejection of claims 2-4, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42-44 made in paragraph 15(b) of the Office Action mailed 08/20/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and above.

Rejection(s) Withdrawn

7) The rejection of claim 1 and those claims dependent therefrom made in paragraph 16 of the Office Action mailed 08/20/03 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the base claim.

8) The rejection of claims 1-3, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42 made in paragraph 18 of the Office Action mailed 08/20/03 under 35 U.S.C § 102(e) as being anticipated by Knudsen *et al.* (WO 98/58953), is withdrawn in light of Applicants' amendment to the base claim. Applicants are asked to note the modified rejection made below to cover the claims as amended.

9) The rejection of claims 42, 43 and 44 made in paragraph 19 of the Office Action mailed 08/20/03 under 35 U.S.C. § 103(a) as being unpatentable over Knudsen *et al.* (WO 98/58953) in view of Murdin *et al.* (US 6,403,101), is withdrawn in light of Applicants' amendment to the base claim. Applicants are asked to note the modified rejection made below.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office. The new rejections are necessitated by Applicants' amendment.

Rejection(s) under 35 U.S.C § 112, First Paragraph

10) Claims 1-4, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42-44 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the claimed polynucleotide 'at least 95% homologous to the nucleotide sequence of SEQ ID NO: 1' or that hybridizes under the recited conditions with SEQ ID NO: 1 (i.e.,

polynucleotide variant or fragment) in the instant claims does not exist independent of its function, i.e., the ability to induce an immune response in a mammal against infection by said strain of *Chlamydia*. The specification discloses diagnostic applications or vaccine intentions for the claimed polynucleotide. However, the instant specification fails to teach a single such 'variant' or 'fragment' of the polynucleotide concurrently having the ability to induce an immune response in a mammal against infection by any strain of *Chlamydia*. Diagnostic or vaccine applications minimally require an ability to elicit a specific immune response or bind specifically to an antibody. The precise structure or relevant identifying characteristics of each DNA 'variant' or 'fragment' as recited having the recited functional activity can only be determined empirically by actually making every DNA molecule and testing each varied DNA molecule to determine whether it has the particularly disclosed protective activity. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention includes a polynucleotide variant or fragment as recited is insufficient to meet the adequate written description requirement of the claimed invention. The polynucleotide of SEQ ID NO: 1 or a protein encoded by the polynucleotide has specific biologic properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide encoded, and the function of the encoded polypeptide. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the claimed DNA fragment or variant. Applicants have not shown that variation or modification of a reference DNA sequence as claimed would automatically predict the production of a polynucleotide variant having the recited functional activity, i.e., the ability to induce an immune response in a mammal against chlamydial infection. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of polynucleotide molecules, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of a polynucleotide of SEQ ID NO: 1, a skilled artisan cannot envision the detailed chemical structure of all the polynucleotide variant species

encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. The nucleic acid variant or fragment itself is required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

11) Claims 1-4, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42-44 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide of *Chlamydia pneumoniae* comprising the nucleotide sequence of SEQ ID NO: 1, does not reasonably provide enablement for a chlamydial polynucleotide that is at least 95% homologous to the nucleotide sequence of SEQ ID NO: 1 (i.e., polynucleotide variant) having the ability to induce an immune response in a mammal against infection by the same strain of *Chlamydia*, as claimed.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a polynucleotide of SEQ ID NO: 1, its 95% sequence homolog, or a polynucleotide that hybridizes with the same under the recited conditions. The polynucleotide claimed is required to induce an immune response against infection caused by a strain of *Chlamydia* when administered in an immunogenically-effective amount to a mammal. Example 3 states that the naked DNA was administered intranasally or intramuscularly to mice which were later challenged with a sublethal dose of *C. pneumoniae*. Whether the polynucleotide itself is a protective antigen which induces polynucleotide-specific antibodies and interacts somehow with the intracellular DNA after gaining access inside the cells, or whether the

administered naked DNA somehow get expressed, with or without a host promoter, *in vivo* in the mammalian subject to produce a polypeptide that is immunogenic and which induces protective immune response against the sublethal challenge, is not known or described. There is absolutely no evidence within the instant specification that a polynucleotide variant as explained above was made and was able to induce an immune response against infection by *C. pneumoniae* or any strain of *Chlamydia*. It is unlikely that the claimed polynucleotide alone, i.e., naked DNA, without an appropriate promoter would express any polypeptide or a part of a polypeptide in a mammalian host. Anti-polynucleotide antibodies, if formed by the polynucleotide alone in the mammalian host, would be unlikely to be inaccessible to the intracellular DNA. With regard to the 95% homologs of the claimed polynucleotide, the specification provides no guidance as to which specific nucleotide bases must be retained in a variant or fragment, or which may be varied without causing any detrimental effect to the claimed polynucleotide that is meant for inducing an immune response in a mammal against a strain of *Chlamydia*. There is no information in the instant specification with regard to which nucleotide variations, i.e., insertions, deletions, additions and substitutions, in the polynucleotide would result in a variant or homolog polynucleotide that would retain the functional integrity or biological/immunogenic competence of the native polynucleotide, without rendering it non-functional. This is important because the art reflects unpredictability as to which nucleotide bases in a specific polynucleotide that encodes a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of the specific protein encoded. While it is known in the art that variation is possible in a given polynucleotide or protein, the exact position within its sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the molecule's functional integrity, is not certain. A random replacement affecting the protective epitopic positions that are critical, for example, to the three-dimensional conformational structure and specific binding property of the molecule, would result in a polynucleotide or the encoded polypeptide that may be non-functional (i.e., non-immunogenic) or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions of a polypeptide encoded by a polynucleotide could result in a molecule which may induce an antibody that may not recognize or bind to the native microbial molecule. In the instant case, this is important because one of the purposes of the instant invention is to produce a chlamydial polynucleotide in its biologically active, immunogenic and/or protective form for inducing an immune response. The instant disclosure lacks guidance on the precise position(s), nature and extent of replacements or variations that can be made in the claimed polynucleotide in order to produce a variant or a homolog, and with regard to whether it would serve as an immunogen capable of conferring immunity to chlamydial infections in a mammalian animal host. There is no predictability that a polynucleotide having as much as at least 5% dissimilarity with SEQ ID NO: 1 would even remain chlamydia-specific and optimally immunogenic and protective. Therefore, undue experimentation would have been required to reproducibly practice the full scope of the invention as claimed currently, due to the lack of adequate and specific guidance, the lack of evidentiary support in the specification enabling the claimed polynucleotide variant as a protective antigen, the nature of the invention, the state of the prior art, the quantity of experimentation necessary and the art-demonstrated unpredictability in determining variations that are acceptable. *Ex parte Foreman*, 230 USPQ 546, 547 (Bd. Pat. Appls. And Interf. 1986). The production and use of a chlamydial polynucleotide homolog that is capable of inducing an immune response against infection by homologous or heterologous chalmydial strain is well outside the realm of routine experimentation. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 102

12) Claims 1-3, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42 are rejected under 35 U.S.C § 102(e)(1) as being anticipated by Knudsen *et al.* (WO 98/58953, already of record).

Knudsen *et al.* disclosed a DNA sequence that shows more than 95% structural sequence homology with the instantly recited SEQ ID NO: 1, an expression vector, and a eukaryotic or human

muscle cell, prokaryotic or bacterial host cell, or recombinant bacteria, such as *E. coli*, or a live microbial vaccine comprising the same. Diagnostic kits comprising one or more nucleic acid fragments are taught. See the attached sequence alignment; and pages 8, 20, 21, 26, 27, 45 and 46 of Knudsen *et al.* The DNA sequence and the protein encoded by the same are used as vaccine components. The vaccine effects *in vivo* expression of the protein in a mammal, such as, a human, to whom it is administered and confers substantially increased resistance to infections with *Chlamydia pneumoniae* (see abstract; and pages 20, 21 and 26). The gene is operably linked to a promoter and is expressed in fusion with a second DNA (see pages 21 and 22; and Example 2). The prior art DNA sequence of such a length and such a high sequence identity is expected to hybridize under the recited hybridizing conditions with the polynucleotide recited in part (c) of claim 1. That the prior art DNA would have the recited function, i.e., the ability to induce an immune response against infection by the chlamydial strain is inherent from the teachings of Knudsen *et al.*

Claims 1-3, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42 are anticipated by Knudsen *et al.*

Rejection(s) under 35 U.S.C. § 103

13) Claims 42, 43 and 44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Knudsen *et al.* (WO 98/58953, already of record) in view of Murdin *et al.* (US 6,403,101, already of record).

Claim 42 is included in this rejection since claims 43 and 44 include the limitation 'claim 42'.

The references of Knudsen *et al.* or Murdin *et al.* are used in this rejection because they qualify as prior art under subsection (e) of 35 U.S.C § 102 and accordingly are not disqualified under U.S.C 103(a).

The disclosure of Knudsen *et al.* is explained above, which does not expressly teach adenoviral or alphaviral vector, or a *Shigella* or *Salmonella* vector.

However, the use of such viral or bacterial vaccine vectors was conventional in the art for the expression of a chlamydial nucleic acid. For instance, Murdin *et al.* taught that chlamydial polynucleotides can be recombinantly expresses in live adenoviral or alphaviral vector, *Shigella* or *Salmonella* vectors (see column 5, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Murdin's adenoviral vector or *Salmonella* vector to express Knudsen's

polynucleotide to produce the vaccine vector of the instant invention, with a reasonable expectation of success, because it was conventional in the art to use an adenoviral or a *Salmonella* vector to express a chlamydial polynucleotide, as shown by Murdin *et al.* The use of alternative and art known live vectors for expression of an art-known polynucleotide is well within the realm of routine experimentation.

Claims 42, 43 and 44 are *prima facie* obvious over the prior art of record.

Remarks

14) Claims 1-4, 10-14, 16, 18, 19, 25, 26, 38, 39 and 42-44 stand rejected.

15) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347 until January 2004 and (571) 272-0854 beginning February 2004. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909 or (521) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER